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Extended Summaries SCI Pesticides Group and RSC Biological and Medicinal Chemistry Group Symposium: Advances in the Chemistry of Crop Protection

The following are extended summaries based on papers presented at the meeting 'Advances in the Chemistry of Crop Protection' organised by P. J. Crowley, G. Mitchell, G. Keen, J. Pickett and P. D. Riordan on behalf of the SCI Pesticides Group and the RSC Biological and Medicinal Chemistry Group and held on 9–11 September 1996 at Churchill College, Cambridge. The contents are entirely the responsibility of the authors and do not necessarily reflect the views of the Editorial Board of Pesticide Science.

α-Hydroxyarylacetamides: A New Class of Fungicidally Active Compounds

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The synthesis and subsequent discovery of fungicidally active α-hydroxyarylacetamides originated from a report that phenyltartronic acid amides exhibited insecticidal activity.[1] The slow-acting nature of this activity led us to speculate that these compounds might be metabolically activated via hydrolysis and then decarboxylation of one of the amide moieties. Subsequently, a synthesis programme looking at a wide range of α-hydroxy-arylacetamides was instigated. This yielded, not a new insecticide, but a novel class of fungicidally active compounds of which compound **1** (Fig. 1) was an early example.[2,3] A systematic study of the optimal substitution patterns in the two phenyl rings indicated that, while various electron-withdrawing groups in the 4- or 3,4-position of the mandelic acid ring gave good activity, very little change was allowed in the phenethylamine ring. One of the best analogues was compound **3** which showed very good activity (>95% control at 50 mg litre^{-1}) against both vine downy mildew (*Plasmopara viticola* Berl. & De Toni) and potato late blight (*Phytophthora infestans* (Mont.) de Bary.

During the next stage of our optimisation studies we systematically sought to modify the bridge connecting the two phenyl rings. This work resulted in the discovery of the biologically interesting methyl-substituted analogues **4** and **5**. The phenylisopropylamide **5** showed the best overall activity seen to date, and we were keen to investigate whether or not there was any biological discrimination between the four stereoisomers. The isomers were separated using chiral HPLC and the highest activity with respect to late blight was found to be associated with the two isomers possessing the *R*-configuration at the phenylisopropylamide centre (Table 1). This suggests that, for this pathogen, this chiral centre is biologically more important than that associated with the mandelamide end of the molecule. The absolute configuration of the phenylisopropylamine was assigned via an asymmetric synthesis.[4]

The two aryl groups of the α-hydroxyarylacetamide structure are joined by six bonds, of which only one, the amide bond, has any conformational restriction on rotation. When such a non-rigid molecule binds at an enzyme or receptor there is an entropy penalty which must be paid in terms of lowered binding affinity due to loss of free rotation. Consequently, reducing the number of free rotations, for example by introducing a double bond into a chain, can lead to an increased binding affinity at the molecular site of action.[5] The preferred conformations of our compounds were studied using

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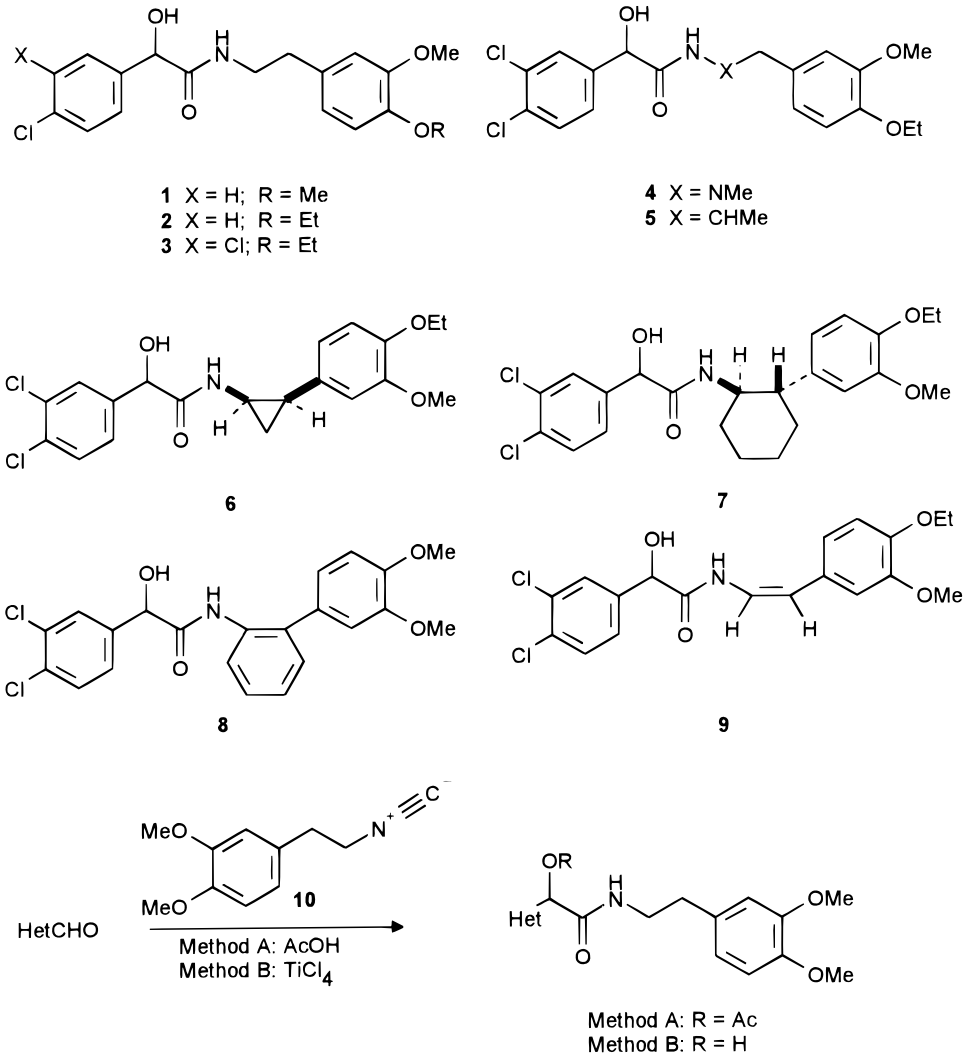

Fig. 1. Structure and synthesis of α-hydroxyarylacetamides.

computational (MOPAC AM1 with Chem X) and NMR (Rate of nOe buildup, DMSO as solvent) techniques. The nOe studies, which were performed on compound **2**, proved particularly informative and provided enough information to enable construction of a 3-D model which accounted for the majority of the observed nOe signals (Fig. 2).

In order to test whether or not the nOe derived structure had any biological relevance in terms of binding at the molecular site of action, we synthesised compounds

TABLE 1
Fungicidal Activity of Compound **5** and its stereoisomers

	% *Protectant control* (*mg litre*$^{-1}$)			
	Phytophthora infestans		*Plasmopara viticola*	
	2·5	*1·25*	*2·5*	*1·25*
Diastereomeric mixture[a]	92	83	100	100
(*R*)-α-Methyl-enantiomer A	100	83	100	99
(*S*)-α-Methyl-enantiomer ent-A	0	0	79	54
(*R*)-α-Methyl-enantiomer B	42	50	64	64
(*S*)-α-Methyl-enantiomer ent-B	21	0	69	75
Dimethomorph	100	90	100	95

[a] 1 : 1 mixture of racemates (A + ent-A) and (B + ent-B).

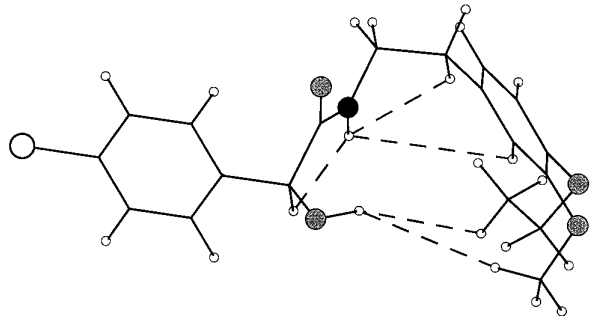

Fig. 2. nOe Derived structure of compound **2**. Important through-space interactions are shown as dashed lines.

6–**9**. All four structures showed reasonable overlap with the nOe structure but the best overlap was shown by the *cis*-cyclopropylamide **6** which encouragingly also showed the best biological activity. Just as importantly the *trans*-isomer of **6**, which did not overlap with the nOe structure, was essentially inactive. In the case of the cyclohexylamide **7** it was the *trans*-isomer which was most active and showed the best overlap. The anilide **8** showed moderate fungicidal activity but surprisingly the related *cis*-eneamide **9**, which overlapped relatively well with the nOe structure, was inactive. Overall, the good biological activity found for the *cis*-cyclopropylamide derivative **6** (comparable to the open-chain compounds) suggests that the nOe derived solution structure is close to that bound at the molecular site of action.

Early structure optimisation work indicated that α-hydroxyheteroarylacetamides were biologically interesting compounds. However, depending on the heterocycle, our existing synthesis routes[2] often failed or were low-yielding. Consequently, a new and more general route was required and the Passerini reaction, involving the reaction of an aldehyde with an isonitrile and a carboxylic acid to give an α-acetoxyacetamide in a single step was investigated. The reaction is well known for benzaldehydes but there is only limited precedent in the literature for its use with heteroaromatic aldehydes.[6–8] The isonitrile **10**[9] was found to react under classical Passerini conditions in the presence of acetic acid with various pyridine, quinoline, pyrimidine, pyrazine and quinoxaline aldehydes to give the required α-acetoxyheteroarylacetamides in 20–50% yield (Fig. 1). Alternatively, the isonitrile **10** could be formed and used *in situ* by dehydration of the *N*-formylphenethylamine with triphosgene.[10] In this case the reaction did not proceed using acetic acid, but worked well in the presence of $TiCl_4$[11] with variously substituted thiophene, thiazole, pyrazole, pyrimidine and 1,2,3-triazole aldehydes to give directly α-hydroxyheteroarylacetamides in 40–80% yield (Fig. 1).[3] Although, in general, this variant gave higher product yields than obtained under classical Passerini conditions, it failed with pyridine aldehydes.

In conclusion, α-hydroxyarylacetamides represent a new class of fungicide with excellent activity against vine downy mildew and late blight. The compounds exhibit good activity against metalaxyl-resistant strains and show long-lasting protectant, curative and translaminar activity. There are indications that they may have a novel mode of action.

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